Adams, J. C. (2020). The Kynurenine connection: how exercise shifts muscle tryptophan metabolism and affects energy homeostasis, the immune system, and the brain. *AJP - Cell Physiology*. https://doi.org/10.1152/ajpcell.00108.2020

Editorial

Title

"The Kynurenine connection: how exercise shifts muscle tryptophan metabolism and affects energy homeostasis, the immune system, and the brain"

Josephine C. Adams,
School of Biochemistry,
University of Bristol,
Bristol BS8 1TD, UK.

Jo.adams@bristol.ac.uk.

Since 2016, *AJP-Cell Physiology* has published two research papers that reported investigations into molecular components of the kynurenine pathway in humans and the possible effects of exercise [1, 3]. Both papers received extraordinary attention in the media and from researchers. For example, in addition to high citation of the 2016 paper [3], as of late March 2020 both papers are in the top five of all publications from *AJP-Cell Physiology* that have been tracked by "Altmetric" criteria (a total of 1746 articles to date). This puts both articles in the top 5% of the 14,380,293 research outputs scored by the "Altmetric" database. Why have these papers commanded so much attention?

Alongside the physical benefits of exercise there is increasing evidence for psychological benefits; this has resulted in the promotion of exercise as a behavioural treatment for depression and other mental health challenges. However, the molecular mechanisms by which exercise-driven changes in the physiological status of skeletal muscle affect cell functions in the central nervous system remain unclear and under investigation. One pathway that is of increasing interest is the so-called kynurenine pathway, which is responsible for degrading 95% of free tryptophan [2]. Transcription factors in skeletal muscle cells, that control the expression of enzymes within this pathway, have been found to be up-regulated as a consequence of exercise, indicating that exercise likely leads to increased flux through the pathway. The first metabolite in the pathway is kynurenine and further metabolism of kynurenine can take place via two pathway branches, one of which generates neurotoxic metabolites. Great translational interest stems from data that increased abundance of the neurotoxic downstream metabolite quinolinic acid in cerebrospinal fluid or plasma correlates with symptoms of depression.

The papers published in *AJP-Cell Physiology*, along with others in the field, investigated the relationship between exercise and molecules relevant to the kynurenine pathway. Schlittler et al. [3] reported that after an endurance exercise regime, the abundance of kynurenine aminotransferase enzymes that metabolise kynurenine along the alternative, neuroprotective pathway, were increased in human skeletal muscle. The results strengthened support for the idea that an increase of kynurenine metabolism along this pathway within muscle could potentially prevent an elevation of neurotoxic metabolites

in the central nervous system. The paper by Allison et al. [1] investigated the specific issue of exercise in older adults and showed that the abundance of key transcription factors controlling kynurenine aminotransferase expression and the kynurenine aminotransferases themselves was increased in skeletal muscle samples after an exercise regime [1]. Thus these papers provided further evidence implicating modulation of the kynurenine aminotransferase pathway as a consequence of exercise.

Given the complexity of the kynurenine pathway itself, the different physiological effects of acute or endurance exercise regimes and the current limited understanding of how kynurenine production in skeletal muscle affects the functions of other tissues and cell types, many outstanding unanswered questions remain. Nevertheless, the importance of further investigations is clear, especially as kynurenine has also been reported to have effects on energy consumption in adipose tissue, cardioprotection and modulation of inflammatory response. It is likely that other functions remain to be discovered. With the goal of promoting research communications in this area, the senior Editors of *AJP-Cell Physiology* are pleased to publish this invited Review by Dr. Jorge Ruas and colleagues [2]. The authors review current knowledge of the molecular components of the tryptophan-kynurenine metabolic pathway and effects of exercise on this pathway, and provide a perspective on current knowns and unknowns regarding the biological effects of kynurenine pathway metabolites on skeletal muscle and other cell types. We thank the authors for this stimulating contribution and welcome further research article submissions from this growing field.

References

1. David J. Allison, Joshua P. Nederveen, Tim Snijders, Kirsten E. Bell, Dinesh Kumbhare, Stuart M. Phillips, Gianni Parise, and Jennifer J. Heisz (2019). Exercise training impacts skeletal muscle gene expression related to the kynurenine pathway. American Journal of Physiology-Cell Physiology 316 (3) 2019 Mar 05
https://doi.org/10.1152/ajpcell.00448.2018

2. Martin L, Azzolini M, and Ruas JL (2020). The Kynurenine connection: how exercise shifts muscle tryptophan metabolism and affects energy homeostasis, the immune system, and the brain. American Journal of Physiology-Cell Physiology, doi

3.Maja Schlittler, Michel Goiny, Leandro Z. Agudelo, Tomas Venckunas, Marius Brazaitis, Albertas Skurvydas, Sigitas Kamandulis, Jorge L. Ruas, Sophie Erhardt, Håkan Westerblad, and Daniel C. Andersson (2016). Endurance exercise increases skeletal muscle kynurenine aminotransferases and plasma kynurenic acid in humans. Am J Physiol Cell Physiol, 310 (10), C836-40. doi.org/10.1152/ajpcell.00053.2016